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2024 American College of Rheumatology (ACR) Guideline for the Screening, Treatment, and Management of Lupus Nephritis

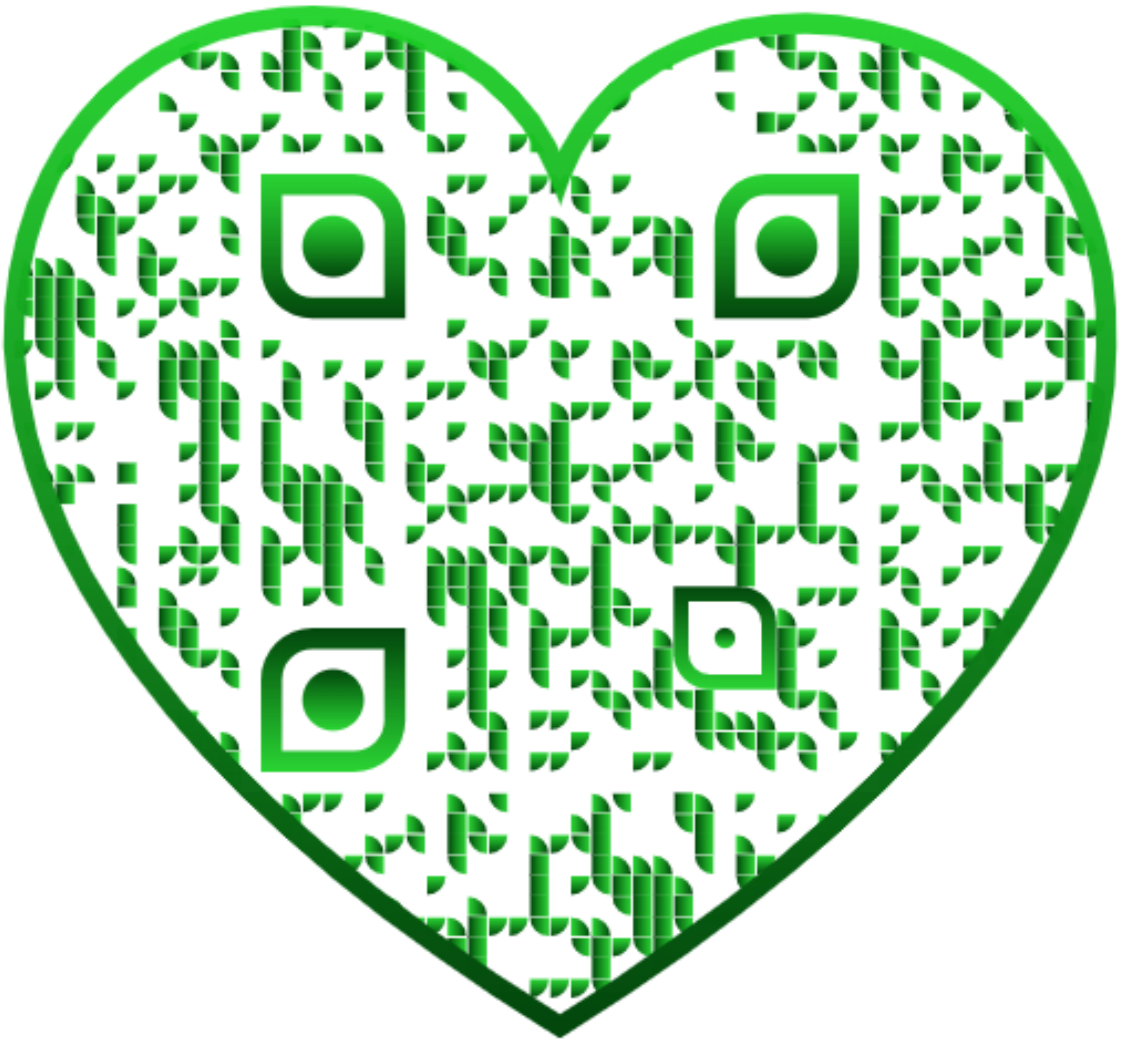
Guideline Summary

This guideline provides evidence-based and expert guidance for the screening, treatment, and management of lupus nephritis (LN) in both adults and children.

The goals of LN treatment are to preserve kidney function and reduce morbidity and mortality of chronic kidney disease while minimizing medication-related toxicities. People with LN should receive collaborative care from rheumatology and nephrology specialists whenever possible. Shared decision-making between clinicians and patients is essential, as it respects patient values and preferences, leading to better adherence and outcomes. Healthcare disparities impact outcomes in people with LN; implementation of treatment recommendations is aimed to alleviate health disparities. We present 28 graded recommendations (7 strong, 21 conditional) and 13 ungraded, consensus-based good practice statements (GPS).

Lupus Nephritis Screening and Treatment Recommendations and Good Practice Statements
SCREENING:
In people with SLE without known kidney disease, we strongly recommend screening for proteinuria at least every 6-12 months, OR when experiencing extra-renal flares.
KIDNEY BIOPSY:
*GPS: **Prompt** kidney biopsy should be performed in people with SLE when LN is suspected (unless contraindicated/not feasible).*
In people with SLE who have proteinuria >0.5 g/g and/or impaired kidney function not otherwise explained, we conditionally recommend performing a kidney biopsy.
For people with treated LN in remission who present with suspected LN flare (increased proteinuria, hematuria, and/or worsening kidney function), OR for people with ≥6 months of appropriate treatment and ongoing/worsening proteinuria, hematuria, and/or decreased kidney function, we conditionally recommend repeat kidney biopsy.

TREATMENT OF ACTIVE LN (CLASS III/IV OR CLASS V):
GPS: Prompt glucocorticoid treatment should be administered for suspected LN to suppress acute inflammation while awaiting a kidney biopsy and histopathology results.
GPS: Dosage of LN medications should be adjusted in people with decreased GFR at initiation of therapy and periodically.
GPS: Adjunctive treatment with systemic anticoagulation for people with LN and significant risk factors for thrombosis (e.g., low serum albumin in context of severe proteinuria) should be discussed with nephrology.
IN PEOPLE WITH ACTIVE/NEW ONSET/FLARE OF CLASS III/IV OR CLASS V:
...If not on HCQ, we strongly recommend initiation and continuation of HCQ to manage and prevent lupus clinical manifestations, unless contraindicated.
...With any elevation in level of proteinuria, including <0.5g/g, we conditionally recommend the addition of RAAS-I.



…We conditionally recommend pulse intravenous glucocorticoids 250-1000 mg methylprednisolone daily x 1-3 days, followed by oral glucocorticoid ≤0.5 mg/kg/day (maximum dose 40 mg/day) with taper to a target dose of ≤5mg/day by 6 months.
… Who have achieved/sustained a complete renal response after treatment with any (triple or dual) immunosuppressive therapy, we conditionally recommend a total duration of therapy of at least 3-5 years.

IN PEOPLE WITH ACTIVE/NEW ONSET/FLARE OF CLASS III/IV (WITH OR WITHOUT CLASS V):
… We conditionally recommend a TRIPLE immunosuppressive regimen consisting of pulse intravenous glucocorticoids 250-1000 mg methylprednisolone daily x 1-3 days, followed by oral glucocorticoid ≤0.5 mg/kg/day (maximum dose 40 mg/day) with taper plus: **a) MPAA plus belimumab -or-** **b) MPAA plus CNI -or-** **c) Euro Lupus Nephritis Trial (ELNT) low-dose CYC plus belimumab (MPAA substituted for CYC after CYC course complete).**
… We conditionally recommend an MPAA-based regimen over a CYC-based regimen.
… With proteinuria ≥3g/g, we conditionally recommend a TRIPLE immunosuppressive regimen that contains MPAA plus CNI.
… With extra-renal manifestations, we conditionally recommend a TRIPLE immunosuppressive regimen that contains belimumab.
… Receiving a CYC regimen, we conditionally recommend ELNT low-dose CYC over a high-dose monthly pulse IV regimen; we also strongly recommend ELNT low-dose CYC over a daily oral CYC regimen.
… Who have undergone TRIPLE immunosuppressive therapy and achieved a <u>complete</u> renal response, we conditionally recommend continuing the same immunosuppressive regimen.
… Who have undergone TRIPLE immunosuppressive and achieved a <u>partial</u> renal response, we conditionally recommend individualizing therapy depending on clinical factors that include the trajectory of response.
…Who have undergone DUAL immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a <u>complete</u> renal response, we conditionally recommend continuing therapy with MPAA (over AZA).
… Who have undergone DUAL immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a <u>partial</u> renal response, we conditionally recommend escalating therapy to a TRIPLE immunosuppressive regimen.

IN PEOPLE WITH ACTIVE/NEW ONSET/FLARE OF PURE CLASS V:
…With proteinuria ≥1 g/g we conditionally recommend treatment with a TRIPLE immunosuppressive regimen consisting of pulse intravenous glucocorticoids 250-1000 mg methylprednisolone daily x 1-3 days, followed by oral glucocorticoid ≤0.5 mg/kg/day (maximum dose 40 mg/day) with taper and MPAA plus CNI.
… With proteinuria <1 g/g, we conditionally recommend treatment with glucocorticoids and/or immunosuppressant therapy (MPAA, AZA, or CNI).

IN PEOPLE WITH NONRESPONSIVE OR REFRACTORY LN:
GPS: Medication dose and patient adherence should be assessed as an important first step in evaluating inadequate response or refractory LN, as insufficient treatment is an important cause of non-response.
In people with any LN class with an inadequate renal response (i.e., have not achieved at least a partial renal response by 6-12 months) we conditionally recommend escalation of treatment: • **For initial DUAL therapy, escalate to TRIPLE therapy.** • **For initial TRIPLE therapy, change to an <u>alternative</u> TRIPLE therapy or consider addition of an anti-CD20 agent as a second immunosuppressive.**
In people with any LN class with refractory disease (i.e., failed two standard therapy courses), we conditionally recommend treatment escalation to a more intensive regimen, including addition of anti-CD20 agents, or combination therapy with three non-glucocorticoid immunosuppressives (i.e., MPAA, belimumab and CNI), or referral for investigational therapy.

OTHER LUPUS KIDNEY DISEASE:
GPS: Alternative etiologies of kidney dysfunction in people with SLE should be carefully excluded, including non-inflammatory etiologies such as hypertensive, diabetic, and medication-induced nephropathy.

ADJUNCTIVE/NON-IMMUNOLOGIC TREATMENT:
*GPS: Adjunctive and non-immunologic therapies and practices should be initiated in addition to appropriate immunosuppressive therapy to improve overall kidney health. Management of cardiovascular health, bone health, infection risk, and reproductive concerns should be addressed.**
GPS: In children with childhood-onset SLE (cSLE) and LN, glucocorticoid regimens should be reduced to pediatric-appropriate doses for children, as reduction of cumulative glucocorticoid dosing is critically important given the early age of onset in cSLE and attendant co-morbidities.
GPS: In children with cSLE and LN, clinicians should monitor for delayed pubertal onset and decreased growth velocity that can result from disease activity and glucocorticoid treatment and consider referral to pediatric endocrinology if indicated.
GPS: For children with cSLE, a structured, intentional transition from pediatric to adult rheumatology care is indicated to avoid poor outcomes during this vulnerable period.
GPS: For older people with LN, medication number, type, and dosage should be regularly assessed, given the risks of polypharmacy and age-related decline in GFR in this population.

*See ACR Guidelines on Vaccination, Glucocorticoid-Induced Osteoporosis and Reproductive Health

[Bass AR, Chakravarty E, Akl EA, et al. 2022 American College of Rheumatology guideline for vaccinations in patients with rheumatic and musculoskeletal diseases. Arthritis Care & Research. 2023 Mar;75(3):449-64; Humphrey MB, Russell L, Danila MI, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis & Rheumatology. 2023 Dec;75(12):2088-102; Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis & Rheumatology. 2020 Apr;72(4):529-56.]

MONITORING:
In people with LN who have not achieved complete renal response, we strongly recommend quantifying proteinuria at least every 3 months.
In people with LN with sustained complete renal response, we strongly recommend quantifying proteinuria every 3-6 months.
GPS: In people with LN, serum complement levels and anti-dsDNA antibody concentrations should be checked at every clinic visit but not more frequently than monthly.

RENAL REPLACEMENT THERAPIES:
GPS: Decisions for initiation and type of dialysis and timing for kidney transplant require close collaboration with nephrology.
In people with LN and ESKD, we strongly recommend kidney transplantation over dialysis.
In people with LN who have progressive loss of kidney function and are nearing ESKD (eGFR of 15 ml/min/1.73m^2), we conditionally recommend preemptive kidney transplant over dialysis or non-preemptive transplant.
In people with LN and ESKD, we conditionally recommend proceeding with kidney transplantation without requiring complete clinical or serologic remission, provided there is no other major organ involvement.
In people with LN on current dialysis or after kidney transplantation, we strongly recommend regular follow up with rheumatology.

Definitions and abbreviations:

TRIPLE therapy:

GC [pulse intravenous glucocorticoids (250-1000 mg methylprednisolone daily x 1-3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) with taper]

plus 2 additional immunosuppressive therapies, usually:

a) MPAA plus belimumab, -or-

b) MPAA plus CNI -or-

c) ELNT low-dose CYC plus belimumab (MPAA substituted for CYC after CYC course complete)

DUAL therapy:
GC [pulse intravenous glucocorticoids (250-1000 mg methylprednisolone daily x 1-3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) with taper] plus
one additional immunosuppressive therapy, usually MPAA or ELNT low-dose CYC

Anti-CD20 therapy: rituximab or obinutuzumab
AZA: Azathioprine
BEL: Belimumab
CNI: Calcineurin inhibitor therapies (cyclosporine, tacrolimus, voclosporin)
CYC: Cyclophosphamide
ELNT: EuroLupus Nephritis Trial
ESKD: End stage kidney disease
GC: Glucocorticoids
HCQ: Hydroxychloroquine
MPAA: Mycophenolic acid analogs (including mycophenolate mofetil, MMF, and mycophenolic acid, MPA)
RAAS-I: renin-angiotensin-aldosterone system inhibitors (including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists)

Summary:
In this guideline, we emphasize the importance of prompt kidney biopsy and LN treatment and propose triple therapy as the most desirable therapy for LN, preferring MPAA regimens over CYC regimens. We propose a lower dose glucocorticoid regimen to minimize toxicity, with a prednisone goal of ≤5 mg/day by 6 months of therapy, and a total therapy duration of 3-5 years for those achieving complete renal response. Discussion between clinicians and patients is critical because multiple factors impact therapy choice. We do not specify a particular CNI because comparative effectiveness and safety studies are not available, and accessibility may dictate CNI choice.

We encourage shared decision-making with patients with discussion of all therapy options, awareness of pill/medication burden, and close monitoring to reach the shared goals of preservation of kidney function and overall health, as well as optimal quality of life.

This summary was approved by the ACR Board of Directors on November 15, 2024. These recommendations are included in a full manuscript, which will be submitted for publication in Arthritis & Rheumatology and Arthritis Care and Research.

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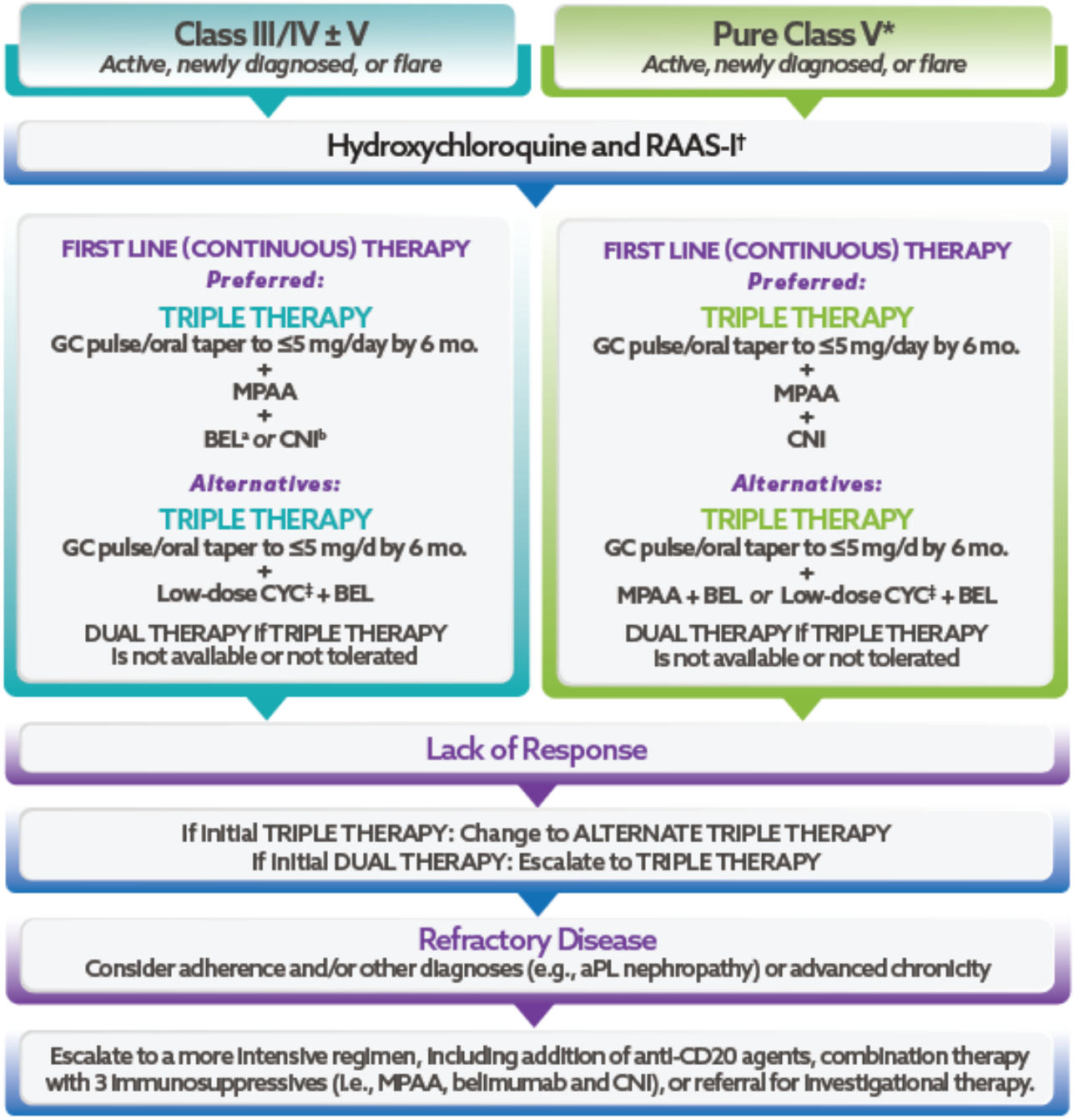
American College of Rheumatology (ACR) 2024 Lupus Nephritis Guideline–Treatment Overview


Class III/IV ± V
Active, newly diagnosed, or flare
Pure Class V*
Active, newly diagnosed, or flare
Hydroxychloroquine and RAAS-I†
FIRST LINE (CONTINUOUS) THERAPY
Preferred:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/day by 6 mo.
+
MPAA
+
BEL[a] or CNI[b]
Alternatives:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/d by 6 mo.
+
Low-dose CYC‡ + BEL
DUAL THERAPY if TRIPLE THERAPY Is not available or not tolerated
FIRST LINE (CONTINUOUS) THERAPY
Preferred:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/day by 6 mo.
+
MPAA
+
CNI
Alternatives:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/d by 6 mo.
+
MPAA + BEL or Low-dose CYC‡ + BEL
DUAL THERAPY if TRIPLE THERAPY Is not available or not tolerated
Lack of Response
If initial TRIPLE THERAPY: Change to ALTERNATE TRIPLE THERAPY
If initial DUAL THERAPY: Escalate to TRIPLE THERAPY
Refractory Disease
Consider adherence and/or other diagnoses (e.g., aPL nephropathy) or advanced chronicity
Escalate to a more intensive regimen, including addition of anti-CD20 agents, combination therapy with 3 immunosuppressives (i.e., MPAA, belimumab and CNI), or referral for investigational therapy.

* For ≥1 g protein; for less than 1 g, treat with GC and/or immunosuppression
† Discuss adjunctive treatment with systemic anticoagulation with nephrology for patients with LN and significant risk factors for thrombosis (e.g., low serum albumin in context of severe proteinuria)
‡ Substitute MPAA once low-dose CYC cycle is completed
a: Recommended preferentially when significant extrarenal manifestations present
b: Recommended preferentially when proteinuria ≥3.0 g

Goal: Complete renal response (CRR)
■ Within 6-12 mo, reduction in proteinuria to ≤0.5 g/g and ■ Stabilization or improvement in kidney function (±20% baseline)
Duration of therapy: at least 3-5 years after achievement of CRR

RAAS-I, renin-angiotensin-aldosterone system inhibitors; GC, glucocorticoid; MPAA, mycophenolic acid analogs (including mycophenolate mofetil, or MMF); BEL, belimumab; CNI, calcineurin inhibitor; CYC, cyclophosphamide.
GC pulse/oral taper: Pulse intravenous glucocorticoids (250-1000 mg methylprednisolone daily x 1-3 days) followed by oral glucocorticoid ≤0.5 mg/kg/day (maximum dose 40 mg/day) and taper.
Low-dose cyclophosphamide: as per ELNT protocol[a], 500 mg IV CYC every 2 weeks for 6 doses.
DUAL THERAPY: GC pulse/oral taper plus one immunosuppressive agent, usually MPAA or low-dose CYC .

[a]Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46:2121-2131.

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